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(54) Title: TREATMENT OF NICOTINE CRAVING AND/OR SMOKING WITHDRAWAL SYMPTOMS WITH A LIQUID NASAL COMPOSITION CONTAINING NICOTINE AND CAFFEINE OR XANTHINE

(57) Abstract

The subject invention encompasses a liquid composition suitable for nasal administration, for the treatment or nicotine craving or smoking withdrawal symptoms comprising nicotine and caffeine or caffeine equivalent.

TREATMENT OF NICOTINE CRAVING AND/OR SMOKING WITHDRAWAL SYMPTOMS WITH A LIQUID NASAL COMPOSITION CONTAINING NICOTINE AND CAFFEINE OR XANTHINE

BACKGROUND OF THE INVENTION

The health hazards from smoking tobacco are well known. Of the many by-products of combustion found in cigarette smoke, the substances most studied have been tars, carbon monoxide, and nicotine. Tars are the agents linked to the causation of various cancers and pulmonary diseases such as emphysema and chronic bronchitis. Carbon monoxide is a deadly gas which reduces the ability of blood hemoglobin to carry sufficient oxygen. Carbon monoxide has also been causally linked to coronary artery disease and atherosclerosis. Nicotine appears to be the most pharmacologically active substance in tobacco smoke, yet it seems not to be as significant from a health standpoint as the tars and carbon monoxide. However, nicotine is the reinforcing substance in tobacco which maintains the addiction.

Various efforts have been made by smokers to discontinue smoking. Chewing beeswax, eating candy and peppermints as well as cold turkey interruption have been tried without much success. The addition of chemicals designed to sicken the user or otherwise render smoking repulsive to the user have also not produced good results. More recent therapies for smoking cessation have focused on the administration of nicotine to the smoker. These therapies allow the individual to satisfy a nicotine habit while minimizing or eliminating side effects caused by absorbing nicotine through the lungs along with the other harmful by-products of combustion of tobacco.

Nicotine supplementation has proven to be an effective therapy as an adjunct to smoking cessation in helping to reduce the craving for smoking and provide relief from smoking withdrawal symptoms. However, there are many smokers for whom nicotine supplementation alone is inadequate. In accordance with the present invention, it has been discovered that a composition can be formulated which provides the combination of nicotine and caffeine or caffeine equivalent in a single therapy. It has also been discovered that such a combination may offer the advantage of providing treatment and/or relief of nicotine craving and/or smoking withdrawal symptoms to a broader spectrum of smokers who wish to break the smoking habit. It has further been discovered that these compositions may also curb the appetite which may aid in reducing the weight gain that is commonly experienced by individuals who stop smoking.

It is an object of the present invention to provide a composition comprising the combination of nicotine and caffeine or caffeine equivalent in a single therapy. It

is also an object of the present invention to deliver the nicotine and caffeine combination therapy in a convenient delivery system. It is a further object of the invention to provide a method for the treatment and/or relief of nicotine craving and/or smoking withdrawal symptoms in individuals who wish to break or decrease the habit of smoking tobacco or the use of any tobacco product. These and other objects will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

The present invention relates to a liquid composition suitable for nasal administration for the treatment of nicotine craving and/or smoking withdrawal symptoms comprising nicotine and caffeine or caffeine equivalent, wherein the composition delivers from about 0.01mg to about 3mg of nicotine, and from about 1mg to about 30mg of caffeine or caffeine equivalent.

The present invention also relates to a method for providing treatment and/or relief of nicotine craving and/or smoking withdrawal symptoms to a human or lower animal in need of such treatment comprising the administration of a safe and effective amount of a liquid composition comprising nicotine and caffeine or caffeine equivalent.

DETAILED DESCRIPTION OF THE INVENTION

The subject invention comprises nicotine, caffeine or caffeine equivalent, and preferably one or more pharmaceutically-acceptable carriers suitable for nasal administration. These compositions are useful for the treatment and/or relief of nicotine craving and/or smoking withdrawal symptoms.

The terms "nicotine craving" and "smoking withdrawal symptoms" as used herein both refer to any physical or psychological reaction relating to breaking the habit of smoking tobacco or using any tobacco product or decreasing the frequency or intensity of smoking tobacco or using any tobacco product.

In general, the descriptive term "pharmaceutically-acceptable" is used herein to describe materials that are non-toxic and suitable for administration to humans and/or lower animals. The term "pharmaceutically-acceptable carrier" as used herein means any material safe and effective for use in the compositions of the present invention. Such materials include pH adjusters, emollients, emulsifiers, buffering agents, solvents, preservatives, agents for regulating isotonicity, water, wetting agents, thickening agents, humectants, surfactants, aromatic compounds, bioadhesive compounds, agents for aiding the film-forming properties and substantivity of the formulations, antimicrobials for maintaining the antimicrobial integrity of the compositions, antioxidants, agents suitable for aesthetic purposes such as fragrances, pigments, and colorings, non-soluble ingredients, and mixtures thereof.

The terms "safe and effective amount", as used herein, mean a sufficient amount of material to provide the desired benefit without undue adverse side effects commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific safe and effective amount will vary with such factors as the particular condition that is being treated, the severity of the condition, the duration of the treatment, the physical condition of the patient, the nature of concurrent therapy (if any), and the specific formulation and optional components hereinafter.

The terms "suitable for nasal administration", as used herein, refer to any formulation that is suitable for the convenient administration of the composition whereby the composition is placed in contact with mucous membranes of the nose and/or the nasal passages.

The following terms will be designated as follows: milligram as "mg", milliliter as "ml", nanogram as "ng", and microgram as "ug".

A detailed description of essential and optional components of the present invention is given below.

Nicotine

The present invention comprises nicotine. Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring. It is a colorless to pale yellow, which is freely water soluble, strongly alkaline, hygroscopic liquid obtained from the tobacco plant. Nicotine has a characteristic odor and turns brown on exposure to air or light [Physicians Desk Reference, 48th Edition, p. 1306, 1984]. Nicotine is delivered in an amount of from about 0.01mg to about 3mg, preferably from about 0.1mg to about 2mg, and most preferably from about 0.5mg to about 1.5mg. Nicotine is also described in Remington's Pharmaceutical Sciences, 18th Edition, 1990, p. 891, which is incorporated herein by reference.

Caffeine

The present inventions also comprise caffeine or a caffeine equivalent. Caffeine is found as white, fleecy masses or long, flexible, silky crystals. It is odorless, bitter tasting, and slightly soluble in water and alcohol. Caffeine may be derived synthetically or by extraction of coffee beans, tea leaves or kola nuts [Hawleys Condensed Chemical Dictionary, Twelfth Edition, 1993]. Examples of suitable sources of caffeine for use in the present invention are pure caffeine, caffeine combined with acetate, citrate, benzoate, phosphate, sulfate or salicylate. Also suitable are any of the xanthine analogues that match caffeine's effectiveness as a central nervous system stimulant, including salts thereof that are compatible. Xanthine derivatives are described in Remington's Pharmaceutical Sciences, 18th Edition, 1990, pp. 1132-34, which is incorporated herein by reference. The caffeine

or caffeine equivalent is delivered in an amount of from about 1mg to about 30mg, preferably from about 3mg to about 20mg, and most preferably from about 5mg to about 10mg.

Pharmaceutically-Acceptable Aqueous Carrier

The invention liquid compositions suitable for nasal administration preferably also contain one or more pharmaceutically-acceptable carriers suitable for nasal administration. Such compositions include (but are not limited to) aqueous nasal solutions for use as drops or as sprays, nasal suspensions, or other liquid formulations suitable administering the present compositions intranasally. Preferred nasal dosage forms are aqueous solutions, emulsions or suspensions which may be administered intranasally as an aerosol or aqueous nasal spray or as nasal drops. Suitable nontoxic pharmaceutically-acceptable carriers are known to those skilled in the art and are also fully disclosed in Remington's Pharmaceutical Sciences, 17th Edition, 1985, which is incorporated by reference herein in its entirety.

While the choice of nasal carrier is not critical to the present invention, the carrier or carriers chosen must be suitable for administering the nicotine and caffeine or caffeine equivalent so that the desired blood levels of these compounds are achieved in the body of the recipient. The desired blood level of nicotine is from about 1ng/ml to about 100ng/ml, preferably from about 5ng/ml to about 75ng/ml, and most preferably from about 10ng/ml to about 50ng/ml, preferably within 1 to 4 hours of administration. . The desired blood level of caffeine or caffeine equivalent is from about 0.01ug/ml to about 20ug/ml, preferably from about 0.1ug/ml to about 15 ug/ml, and most preferably from about 0.5ug/ml to about 10ug/ml, preferably within 1 to 4 hours of administration.

The present compositions will normally be prepared in dosage unit form to contain safe and effective amounts of the nicotine and caffeine (or equivalent) to achieve the desired blood levels. Fractions of the dosage units or multiple dosage units may also be utilized. In general, the liquid compositions herein deliver to a human or lower animal from about 0.01mg to about 3mg, preferably from about 0.1mg to about 2mg, and most preferably from about 0.5mg to about 1.5mg of nicotine; and from about 1mg to about 30mg, preferably from about 3mg to about 20mg, and most preferably from about 5mg to about 10mg of caffeine or caffeine equivalent. Preferably, the present invention may be a liquid composition suitable for nasal administration, for the treatment of nicotine craving or smoking withdrawal symptoms comprising nicotine, caffeine or caffeine equivalent, and one or more pharmaceutically-acceptable carriers suitable for nasal administration, wherein the

composition delivers from about 0.01mg to about 3mg of nicotine and from about 1mg to about 30mg of caffeine or caffeine equivalent.

The amount of nicotine and caffeine or caffeine equivalent and frequency of administration may vary depending on the carrier chosen and the personal needs of the user. However, it is suggested (as an example) that the present invention be administered from about once to about 20 times per day, preferably from about 2 to about 10 times per day and most preferably from about 4 to about 8 times per day. A typical dose for a aqueous nasal spray carrier contains about one to about three sprays per nostril.

The present compositions may contain one or more solvents. Suitable solvents include but are not limited to water, alcohol, propylene glycol, glycerin, sorbitol solution and the like, to assist solubilization and incorporation of water-insoluble ingredients. Preferred for use herein are pharmaceutically-acceptable aqueous saline solution carriers. These solutions which generally contain sodium chloride as the salt are also fully described in Remington's Pharmaceutical Sciences, 17th Edition (1985) p. 835, (incorporated herein by reference). The salt is present in the solution at a level of from about 0.01% to about 2%, preferably from about 0.5% to about 1.0%, and most preferably from about 0.5% to about 0.75%. Purified water is present at a level of from about 90% to about 99.99%, preferably from about 95% to about 99.5% , and most preferably from about 98% to about 99.5%, by weight of the composition.

The compositions of the present invention may be prepared as emulsions. Single emulsion preparations of the oil-in-water type are well-known in the art and are useful in the present invention. Also useful in the present invention are multi-phase emulsion compositions, such as the water-in-oil-water type, (as disclosed in U.S. Patent No. 4,254,105, Fakuda et al., issued March 3, 1981, incorporated herein by reference), the triple emulsion systems comprising an oil-in-water-in-silicone fluid emulsion and microemulsion systems. In general, such single or multiphase emulsions contain water, emollients and emulsifiers. Emulsions are described in detail in Remington's Pharmaceutical Sciences, 17th Edition, pp. 298-308, which is incorporated herein by reference.

The compositions may also comprise from about 0% to about 10%, preferably from about 2% to about 5%, of one or more pharmaceutically-acceptable emulsifiers. These emulsifiers may be nonionic, anionic or cationic. Suitable emulsifiers are disclosed in, for example, U.S. Patent 3,755,560, issued August 28, 1973, Dicert et al.; U.S. Patent 4,421,769, issued December 20, 1983, Dixon et al.; and McCutcheon's Detergents and Emulsifiers, North American Edition, pages 317-324

(1986); the disclosures of which are incorporated herein by reference. Preferred emulsifiers are anionic or nonionic, although the other types may also be used.

The present compositions may also comprise from about 0% to about 10% of a pharmaceutically-acceptable emollient. Suitable emollients include volatile silicone oils, non-volatile emollients such as fatty acid and fatty alcohol esters, highly branched hydrocarbons known as the Permethyl 99 through 108A series (available from Permethyl Corporation), and mixtures thereof. Suitable emollients are disclosed in U.S. Patent No. 5322689, to Hughes et al., issued 6/21/94, incorporated herein by reference.

Most preferably, the compositions are isotonic, i.e., they have the same osmotic pressure as blood and lacrimal fluid. If desired, sustained release compositions, for example, sustained release sprayable solutions and suspensions can be conveniently employed. The desired isotonicity of the compositions of this invention may be accomplished by using, for example, sodium chloride, or other pharmaceutically-acceptable agents such as dextrose, boric acid, sodium tartrate, sodium phosphate, potassium phosphate, propylene glycol or other inorganic or organic solutes. Sodium chloride is preferred particularly for buffers containing sodium ions.

Viscosity of the compositions may be maintained at the selected level using a pharmaceutically-acceptable thickening agent. Methyl cellulose is preferred because it is readily and economically available and is easy to work with. Other suitable thickening agents include, for example, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, and the like. The preferred concentration of the thickener will depend upon the agent selected. The important point is to use an amount which will achieve the selected viscosity. Viscous compositions are normally prepared from solutions by the addition of such thickening agents.

Preferred compositions within the scope of this invention will contain from about 0.01% to about 5% of a pharmaceutically-acceptable humectant to inhibit drying of the mucous membrane and to prevent irritation. Any of a variety of pharmaceutically-acceptable humectants can be employed including, for example, sorbitol, propylene glycol or glycerol. As with the thickeners, the concentration will vary with the selected agent, although the presence or absence of these agents, or their concentration is not an essential feature of the present invention.

Enhanced absorption across the nasal membrane can be accomplished by employing a pharmaceutically-acceptable surfactant. Typical useful surfactants for the present compositions include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Tween 80, Polyoxyl 40 Stearate,

Polyoxyethylene 50 Stearate and Octoxynol, as well as Oxyethylated tertiary octyl phenol formaldehyde polymer (available from Sterling Organics as tyloxapol). The usual concentration is from about 0.5% to about 10% based on the total weight.

A pharmaceutically-acceptable preservative is generally employed to increase the shelf life of the compositions. Benzyl alcohol is suitable, although a variety of preservatives including, for example, parabens, thimerosal, chlorobutanol, phenylmercuric acetate or benzalkonium chloride may also be employed. The most preferred preservative system for use herein comprises a combination of benzalkonium chloride, chlorhexidine gluconate and disodium EDTA. A suitable concentration of the preservative will be from about 0.001% to about 2% based on the total weight, although there may be appreciable variation depending upon the agent selected.

The present invention may also comprise one or more bioadhesive compounds which adhere to moist area of biological membranes. Such compounds include sodium carboxymethylcellulose, amyopectin, hydroxyethylcellulose, acrylates, gelatins, guar gum karaya gum, tragacanth, agar, alginc acid calcium carboxymethylcellulose, dextrin, methylcellulose, pectin, polyethylene glycol and polyvinylpyrrolidone. The bioadhesive compounds may be present at a level of from about 0.1% to about 30%, and preferably from about 7% to about 25%, by weight of the composition.

The compositions of the present invention also include microencapsulation of either the nicotine or caffeine (or caffeine equivalent) or both. Techniques and materials for microencapsulation are well known in the art. Microencapsulation is discussed more fully in Kirk and Othmer's Encyclopedia of Chemical Technology, Vol. 13, 2nd Edition, pp.436-456, which is incorporated herein by reference.

The compositions of the present invention may also contain one or more aromatic components. These aromatics include, for example, menthol, eucalyptol, benzaldehyde (cherry, almond); citral (lemon, lime); neral; decanal (orange, lemon); aldehyde C-8, aldehyde C-9 and aldehyde C-12 (citrus fruits); tolyl aldehyde (cherry, almond); 2,6-dimethyl-octanal (green fruit); 2-dodecenal (citrus, mandarin); thymol; cedar leaf oil, myristica oil, lavender oil, nutmeg oil, turpentine; 3-l-menthoxy propane-1,2-diol; N-substituted-p-menthane-3-carbox-amides and acyclic carboxamides; and mixtures thereof. Preferred are menthol, eucalyptol, thymol, cedar leaf oil, myristica oil, lavender oil, nutmeg oil, turpentine, and mixtures thereof. Aromatic compounds may be present at a level of from about 0.0001% to about 1%, preferably from about 0.001% to about 1%, and most preferably from about 0.001% to about 0.5%, by weight of the compositions.

A variety of additional optional pharmaceutically-acceptable ingredients may also be added to the present invention compositions. These additional ingredients include pH adjusters such as sodium hydroxide; buffering agents such as sodium bicarbonate, sodium phosphate, and potassium phosphate; various polymers for aiding the film-forming properties and substantivity of the formulations; antimicrobials for maintaining the antimicrobial integrity of the compositions; antioxidants; and agents suitable for aesthetic purposes such as fragrances, pigments, and colorings.

The compositions may also contain low levels of pharmaceutically-acceptable insoluble ingredients added, for example, for visual effect purposes, e.g., thermochromic liquid crystalline materials such as the microencapsulated cholesteryl esters and chiral nematic (nonsterol) based chemicals such as the (2-methylbutyl) phenyl 4-alkyl(oxy)benzoates available form Hallcrest, Glenview, Illinois 60025, U.S.A.

The pH of the composition is generally from about 5 to about 10, preferably from about 6 to about 9, and most preferably from about 6.0 to about 8.5.

Method of Treatment

The present invention also encompasses a method of treatment. The method of providing treatment and/or relief of nicotine craving and/or smoking withdrawal symptoms to a human or lower animal in need of such treatment , as, disclosed herein, comprises the administration of a safe and effective amount of a liquid composition suitable for nasal administration comprising nicotine and caffeine or caffeine equivalent. Such compositions preferably further comprise one or more pharmaceutically-acceptable carriers suitable for nasal administration.

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

EXAMPLE I

A nasal composition is prepared by combining the following components utilizing conventional mixing techniques.

Ingredient	Weight %
Tyloxapol	0.70
Sodium Phosphate	0.10
Potassium Phosphate	0.35
Sodium Chloride	0.65

Disodium EDTA	0.01
Caffeine	10.00
Nicotine	1.00
Water, Purified QS	87.19

Tyloxapol and water are added to an appropriately sized vessel and completely mixed under low heat. Ingredients are added one at a time with mixing, allowing each to dissolve before adding the next. The aromatic[s] are blended together in a separate premix before being added to the batch. A separate premix is also made for chlorhexidine gluconate. After all ingredients have been added, purified water is used to bring the batch to the appropriate weight.

EXAMPLE II

A nasal spray composition is prepared by combining the following components utilizing conventional mixing techniques.

Ingredient	Weight %
Pluronic L-44	2.50
Sodium Phosphate	0.10
Potassium Phosphate	0.35
Sodium Chloride	0.65
Disodium EDTA	0.01
Caffeine	10.00
Nicotine	1.00
Water, Purified QS	85.39

Example II was prepared according the disclosure for Example I.

What is Claimed is:

1. A liquid composition suitable for nasal administration, for the treatment of nicotine craving or smoking withdrawal symptoms comprising nicotine and caffeine or caffeine equivalent, wherein the composition delivers:
   a) from 0.01mg to 3mg of nicotine; and
   b) from 1mg to 30mg of caffeine or caffeine equivalent.

2. The composition according to Claim 1 wherein (b) is caffeine.

3. A liquid composition suitable for nasal administration, for the treatment of nicotine craving or smoking withdrawal symptoms comprising nicotine, caffeine or caffeine equivalent, and one or more pharmaceutically-acceptable carriers suitable for nasal administration, wherein the composition delivers:
   a) from 0.01mg to 3mg of nicotine; and
   b) from 1mg to 30mg of caffeine or caffeine equivalent.

4. The composition according to Claim 3 wherein the composition is in the form of an aqueous saline solution comprising from 0.01% to 2% of sodium chloride and from 90% to 99.99% of purified water.

5. The composition according to Claim 4 wherein (b) is caffeine.

6. The composition according to Claim 4 wherein (b) is the caffeine equivalent xanthine.

7. The liquid composition suitable for nasal administration according to Claim 3 comprising:
   a) from 0.1mg to 2mg of nicotine; and
   b) from 3mg to 20mg of caffeine or caffeine equivalent.

8. The composition according to Claim 7 wherein the composition is in the form of an aqueous saline solution comprising from 0.5% to 1.0% of sodium chloride and from 95% to 99.5% of purified water.

9. The composition according to Claim 8 further comprising from 0.5% to 10% of a pharmaceutically-acceptable surfactant.

10. The composition according to Claim 9 further comprising from 0.001% to 2% of a pharmaceutically-acceptable preservative.

11. The composition according to Claim 10 further comprising from 0.01% to 5% of a pharmaceutically-acceptable humectant.

12. The composition according to Claim 11 wherein the composition is in the form of a nasal spray.

13. The composition according to Claim 11 wherein the composition is in the form of nasal drops.

INTERNATIONAL SEARCH REPORT

Inter. al Application No
PCT/US 95/07425

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/52 A61K9/00 //(A61K31/52,31:465)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A,4 778 677 (G.K. EBBESEN) 18 October 1988 see the whole document ---	1-13
Y	TOXICOL APPL PHARMACOL (UNITED STATES), JUN 30 1985, VOL. 79, NO. 2, PAGE(S) 268-73, Tariq M et al 'Effect of nicotine and caffeine pretreatment on the gastric mucosal damage induced by aspirin, phenylbutazone, and reserpine in rats.' see the whole document --- -/--	1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 October 1995	13. 10. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Stierman, B

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INTERNATIONAL SEARCH REPORT

Inter ıal Application No
PCT/US 95/07425

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. OF NEUROCHEMISTRY, vol.61, no.5, 1993 pages 1901 - 1906 Wilson S P 'Pertussis toxin enhances proenkephalin synthesis in bovine chromaffin cells' see the whole document	1-13
Y	DE,A,35 06 406 (STROMBERG H.-J.) 28 August 1986 see the whole document	1-13
Y	PHARMACOL BIOCHEM BEHAV (UNITED STATES), APR 1994, VOL. 47, NO. 4, PAGE(S) 919-36, Cohen C et al 'Caffeine antagonizes EEG effects of tobacco withdrawal.' see the whole document	1-13
Y	US,A,5 051 426 (F.W. PARNELL) 24 September 1991 see the whole document	1-13
Y	US,A,4 568 676 (J.B. SMITH) 4 February 1986 see the whole document	1-13
Y	PSYCHOPHARMACOLOGY (BERL) (GERMANY), JAN 1994, VOL. 113, NO. 3-4, PAGE(S) 438-44, Perkins KA et al 'Subjective and cardiovascular responses to nicotine combined with caffeine during rest and casual activity.' see the whole document	1-13
Y	J ETHNOPHARMACOL (SWITZERLAND), MAR 1985, VOL. 13, NO. 1, PAGE(S) 3-49, 'A multidisciplinary overview of intoxicating snuff rituals in the western hemisphere.' see page 30 - page 31 see page 35 - page 36	1-13
A	ADDICT BEHAV (ENGLAND), MAY-JUN 1994, VOL. 19, NO. 3, PAGE(S) 229-56, Swanson JA et al 'Caffeine and nicotine: a review of their joint use and possible interactive effects in tobacco withdrawal.' see the whole document	1-13

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 95/07425

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.: 1,3,4,7-13
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The expression "caffeine equivalent" does not make sufficiently clear, which compounds are meant. The search has therefore been restricted to the compounds explicitly mentioned in the claims and to the general inventive concept.

3. [---] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inter. ial Application No
PCT/US 95/07425

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-4778677	18-10-88	NONE		
DE-A-3506406	28-08-86	EP-A,B	0192950	03-09-86
US-A-5051426	24-09-91	US-A-	5219858	15-06-93
US-A-4568676	04-02-86	NONE		